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REVIEW ARTICLE

Is Cholesterol Lowering an Alternative to Revascularization in Some Patients With Coronary Artery Disease?

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Cholesterol lowering has been shown to decrease the dimensions of atherosclerotic plaques in some patients with coronary artery disease. Because of this observation, there is growing discussion about whether or not cholesterol lowering might be used in place of revascularization. The available data suggest that cholesterol lowering in place of revascularization may be appropriate for patients with chronic stable angina, for patients who are asymptomatic but have provocable ischemia after myocardial infarction, and for patients at moderate risk for cardiac events as judged by exercise test or clinical variables. The available data do not justify changing current practices; further study is necessary.

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Animal research in the early 1980s demonstrated that lowering serum cholesterol levels can cause regression of experimentally induced atherosclerosis. Quantitative angiography studies published over the last 5 years have extended these observations to humans by showing that lowering cholesterol levels in patients with established coronary artery disease can result in a net improvement in lumen reduction.[1-7] Studies using pharmacologic interventions have shown lower rates of progression for the intervention group compared with the control group (32% vs 54%), as well as higher rates of regression (25% vs 8%).[8] Studies in which there was strict adherence to a low-fat diet that produced cholesterol lowering near that produced by pharmacologic interventions have shown similar results.[1,4] In addition, there is a growing body of evidence to support the hypothesis that cholesterol lowering changes not only the structure of the vessel, but how the vessel functions as well. Cholesterol lowering returns vasomotor response toward normal[9] and may alter lesion architecture in ways that make plaques less likely to fissure and rupture.[10] These studies have changed clinical practice by fueling modification of the goal levels for cholesterol treatment under the National Cholesterol Education Program's guidelines.[11]

Since the introduction of coronary artery bypass grafting (CABG) in the 1960s and percutaneous transluminal coronary angioplasty (PTCA) in the 1980s, a strategy has evolved in which patients judged to be at high risk for subsequent myocardial infarction (MI) or sudden cardiac death are treated with revascularization, and low-risk patients are treated with anti-ischemic medications, as depicted in the **Figure**, top. Patients cross over from one arm of the algorithm to another when those who are being medically treated develop refractory symptoms or when those who have been allocated to the invasive strategy are shown to have anatomy not suitable for revascularization. Implicit in the recommendations of the National Cholesterol Education Program[11] is a modification of the strategy as depicted in the Figure, center, in which cholesterol lowering is used as an adjuvant to revascularization or to anti-ischemic medication.

Some investigators have argued, however, that the clinical studies that demonstrate regression should motivate a broader reassessment of strategies used for treating patients with coronary artery disease.

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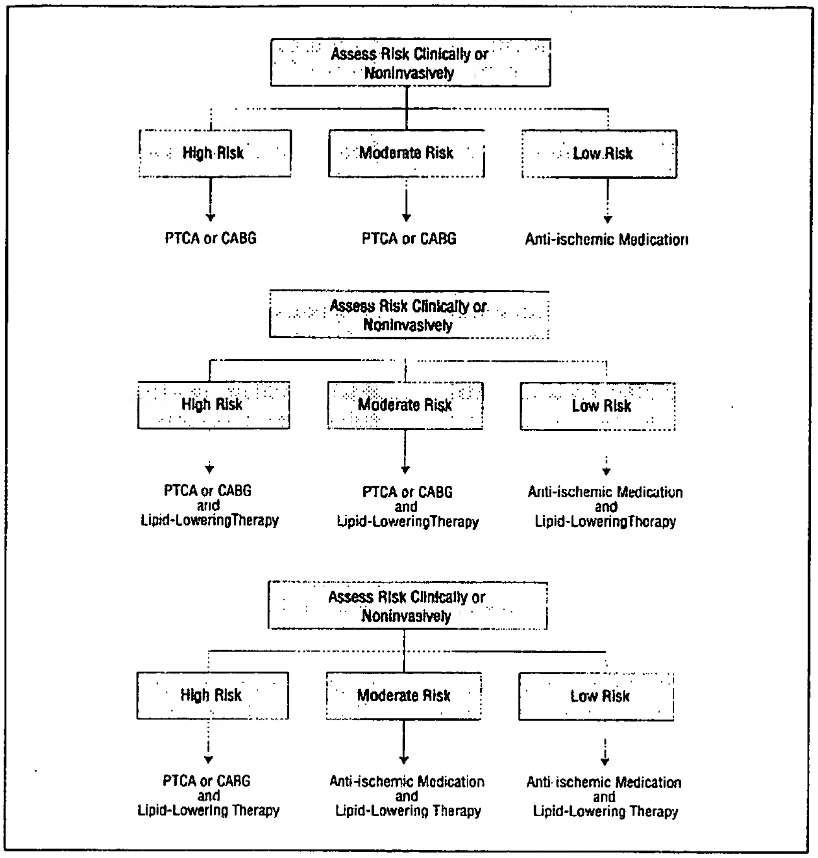

Top, Simplified strategy for the treatment of patients with coronary artery disease. Center, Simplified strategy modified by current recommendations for the treatment of hypercholesterolemia. Bottom, Alternative use of hypercholesterolemia treatment to modify the approach to coronary artery disease. PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

Specifically, they argue that treatment aimed at regression should replace angioplasty or bypass surgery in intermediate-risk patient subgroups, as depicted in the Figure, bottom. Phrased another way, patients should not undergo elective revascularizaton without first having undergone an adequate trial of cholesterol lowering, where adequate is defined as levels similar to those in the quantitative angiographic studies demonstrating stabilization or regression or as a low-density lipoprotein cholesterol level of less than 2.60 mmol/L (100 mg/dL), as suggested by the National Cholesterol Education Program Expert Panel. The duration of such therapy should be at least 6 months.[12] The basis for this argument needs to be reviewed critically.

I will examine the patient groups in which cholesterol lowering might be an alternative to revascularization; weigh the known effects of angioplasty, bypass, and cholesterol lowering on cardiovascular morbidity and mortality in these groups; discuss the effects on total mortality; and finally, examine what is known about the relative costs of these alternate strategies.

IDENTIFYING APPROPRIATE PATIENT SUBGROUPS

Coronary artery disease is encountered clinically as asymptomatic disease, stable angina, unstable angina, or MI. Although it is recognized increasingly that distinctions among these syndromes may be arbitrary, they provide a useful framework for analyzing potential approaches to the disease.

In asymptomatic patients, the natural history of the disease is such that it is unlikely that intervention prior to the onset of symptoms will alter outcome,[13] although studies of such strategies are ongoing.[14] There is a clear imperative for revascularization only with left main coronary artery disease. Cholesterol lowering in asymptomatic patients is therefore not an important alternative to revascularization at present, since revascularization is rarely used.

In patients with unstable angina, the natural history of the disease is such that refractory symptoms require revascularization in at least one third of patients within 2 years of presentation.[15] Because the benefits with cholesterol lowering may require 1 to 2 years of treatment, this form of therapy is not appropriate in unstable angina.

We are left with patients who have stable angina or who have survived an MI. In these groups, revascularization is performed either for relief of symptoms or because of moderate or high risk for subsequent coronary events. Cholesterol lowering might be an alternative in those at low risk with unacceptable symptoms or in those with moderate or high risk regardless of symptoms. I shall consider these three situations separately.

Low-Risk Patients With Refractory Symptoms

How do the results of CABG and PTCA compare with those of cholesterol lowering in patients who are at low risk for cardiac events and who have unacceptable symptoms? The effect of CABG on angina has been well studied. In the European Coronary Surgery Study,[16] 58% of patients randomized to surgery and 14% of patients randomized to medical therapy were free of angina at 1 year. In the Coronary Artery Surgery Study,[17] 52% of the patients with angina who were treated surgically and 15% of those who were treated medically were free of chest pain at 5 years. Statistical analysis in this study removed the effect of crossover from medical to surgical treatment. In the Veterans Administration study,[18] 49% of patients assigned to surgery had a marked improvement in angina at 1 year, whereas 12% of patients assigned to medical therapy had similar relief. By 10 years, however, marked an-

gina relief was present in 33% of the patients in the surgery group and in 37% of those in the medical group. The 10-year results were not statistically significant. Thus, bypass surgery confers significant relief from angina, but this benefit is attenuated at 5 years and absent at 10 years after the procedure. It should be noted that many of the patients in these studies who were surgically treated in the 1970s did not receive internal mammary artery grafts for left anterior descending artery disease. These grafts have higher long-term patency rates than do saphenous vein grafts,[19] and they confer a survival benefit.[20] This change in practice, as well as other improvements in surgical technique and postoperative care, may have improved the 10-year benefits of surgery relative to medical treatment.

Despite the fact that several hundred thousand patients undergo PTCA in the United States each year, to my knowledge only one study has randomly compared medical therapy with angioplasty.[21] In this study, the ACME (Angioplasty Compared to Medicine) Trial, 212 patients with single-vessel disease were randomized to either angioplasty or medical therapy. Only 9% of patients had been free of angina during the 30 days prior to randomization, and no patient's angina was judged to be unstable. Patients were followed up for 6 months. Primary end points in the study were frequency of angina, frequency of nitroglycerin use, and exercise tolerance judged by treadmill time. The decrements in angina and in number of nitroglycerin tablets used were not significantly different between the medical treatment and angioplasty groups. Patients who had undergone angioplasty had a greater improvement in exercise capacity compared with the patients treated medically: exercise time increased 2.1 minutes in the angioplasty patients and 0.5 minutes in the medically treated patients. Sixty-four percent of the patients in the angioplasty group were angina free at 6 months, compared with 46% of those in the medically treated group. However, patients randomized to angioplasty had a higher incidence of the combined end point of need for CABG, MI, and death.

The ACME Trial has been interpreted[22] as demonstrating that angioplasty gives patients with angina modest symptomatic improvement, but the cost is greater exposure to adverse outcome. It should be remembered that these patients have an excellent prognosis with medical therapy. There have been several uncontrolled studies of the efficacy of angioplasty in angina.[23-25] Although inclusion criteria for these studies were less selective and the patient populations less homogeneous, long-term success rates were comparable to those found in the ACME Trial. Follow-up was longer, varying from 1 to 8 years. There are many ongoing comparisons of PTCA and CABG. Preliminary data are available for many of these; formal publication is available for one. The RITA (Randomised Intervention Treatment of Angina) Trial[26] has reported results from 1011 patients who were randomized to either PTCA or CABG and who were followed up for an average of 2.5 years. There were no differences in deaths or in the combined end point of death or nonfatal MI.

Data on the effect of cholesterol lowering on angina are even more scarce than for PTCA. In the Lifestyle Heart Trial,[1] patients were randomized either to conventional treatment or to treatment with a strict vegetarian very-low-fat diet, exercise, and stress reduction. Patients underwent quantitative angiography at baseline and after 1 year of treatment. Symptoms were analyzed. Patients in the experimental group reported reductions of 91%, 42%, and 28% in the frequency, duration, and severity of angina, respectively, while control patients reported increases of 165%, 95%, and 39%. While these data suggest a benefit conferred on angina by cholesterol lowering, they are subject to criticism. There were no objective data, such as exercise testing, and symptoms of angina may be affected by the placebo effect in a study in which blinding is impossible. Gould et al[27] investigated the effects of 90 days of cholesterol-lowering therapy on myocardial ischemia. The study was terminated before enrollment had been completed when funding was withdrawn. Twelve patients with coronary artery disease and stable angina underwent either nutritional or drug treatment of hyperlipidemia, with decreases in total cholesterol from 7.70±1.80 (mean±SD) (29±69 mg/dL) to 5.80±1.85 (224±72 mg/dL) and in low-density lipoprotein cholesterol from 5.50±2.05 (213±79 mg/dL) to 3.90±1.50 (151±59 mg/dL). Using rest-dipyridamole positron emission tomography, Gould and colleagues demonstrated decreases in both the size and the severity of perfusion defects following cholesterol lowering. Their study and the Lifestyle Heart Trial[1] suggest that cholesterol lowering may relieve myocardial ischemia and its symptoms by an as yet undemonstrated mechanism. Gould and colleagues' study is particularly intriguing because improvement occurred after a short treatment period. It is unlikely that reduction in atheroma size occurred over the 90 days. Improvement in vasomotor function in the vessel is one possibility.

In summary, coronary bypass surgery produces excellent control of angina, but the benefit over medical therapy attenuates with time and is not present 10 years after surgery. Angioplasty also controls angina better than does medical therapy in single-vessel disease. To my knowledge, there are no long-term data on symptom control with PTCA, but many investigators believe that the results may be more durable than those with CABG.[2] Data from two small-scale studies of cholesterol lowering in angina are tantalizing but inconclusive; any estimation of long-term effects of cholesterol lowering on angina would be purely speculative. Since patients with stable angina have a good prognosis and available data do not demonstrate a clear benefit of revascularization on mortality, it is reasonable to further consider cholesterol lowering as an alternative to revascularization in patients whose

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Moderate-Risk Patients

How do the results of PTCA and CABG compare with those of cholesterol lowering in patients with coronary disease who are at moderate risk for events? Patients at moderate risk for cardiac events are those who have ischemia provocable on exercise testing or moderate reduction in the left ventricular ejection fraction after MI[28,29] or those without prior MI whose exercise test results predict moderate risk.[30,31] Patients in the moderate-risk group have yearly mortality rates of 2% to 5%. Such patients routinely undergo revascularization in the United States regardless of symptoms. Direct validations of this approach are scarce.

In the Randomized Coronary Artery Surgery Study,[32] a subgroup of patients who were asymptomatic after MI were randomized to surgery or medical treatment. The number of patients treated was small (82 randomized to medical therapy, 78 to surgery), the crossover great, and the group undefined in terms of left ventricular function and presence of ischemia. At the 10-year follow-up, 62% of the patients assigned to initial medical therapy and 68% of the patients assigned to surgery were alive and free of MI. Although these data are subject to several interpretations, it is safe to say they do not demonstrate a large benefit to routine invasive strategy in patients who have had an MI. To my knowledge, there are no data on the specific use of CABG in patients who are at moderate-risk after MI, nor are there data on the specific use of PTCA in patients who have had an MI.

Routine use of cholesterol lowering in patients after MI has been investigated in several trials, which have been reviewed by Rossouw et al.[33] Using meta-analysis, they demonstrated a significant reduction in risk for cardiovascular death and a decrease in risk for total deaths that did not reach statistical significance.

Two studies not included in Rossouw and colleagues' analysis are also relevant. In the Coronary Drug Project,[34] 8341 male survivors of MI were treated with one of five lipid-lowering regimens or with placebo. Three arms of the study were terminated early. For the fourth, clofibrate, no beneficial effect was demonstrated. When patients treated with niacin were followed up 8.8 years after the conclusion of the study, the total mortality rate was significantly lower in the treatment group (52.0%) than in the placebo group (58.2%).

In the POSCH (Program on the Surgical Control of Hyperlipidemias) study,[35] 838 survivors of MI were randomized to either partial ileal bypass or conventional treatment of hyperlipidemia. There were 62 deaths in the control group and 49 in the surgery group; the difference was not statistically significant. When the combined end point of death due to coronary heart disease and nonfatal MI was considered, surgery patients fared better than control patients (82 vs 125 [$P<.001$]).

With respect to patients without prior MI whose exercise test results predict moderate risk, data are again scarce. The European Coronary Surgery Study Group[16] retrospectively compared patients with positive results on exercise tests (ST segment depression >1.5 mm) with patients whose results were negative (ST segment depression <1 mm). There was survival benefit conferred by surgery in the former group but not in the latter. This grouping of patients does not conform exactly to moderate risk by exercise testing as defined above. Data from patients in the Coronary Artery Surgery Study Registry, who were not randomized, come closer.[36] Of the patients with normal left ventricular function, those with positive results on exercise tests or those who could not complete the second stage of the Bruce protocol had better survival if they were treated surgically. No angioplasty study or cholesterol-lowering study provides us with information about the value of these therapies in patients at moderate risk by exercise testing.

The available data suggest that the routine use of cholesterol lowering after MI improves outcome; the routine use of an invasive strategy including revascularization has been inadequately addressed. To my knowledge, there are no data available on targeting either strategy at patients who have provocable ischemia or moderate reductions in the left ventricular ejection fraction after MI. In patients at moderate risk by exercise test results, surgery appears to confer mortality benefit. Again, I know of no data on the use of PTCA or cholesterol lowering in this subset.

The estimated reduction in cardiovascular mortality risk of 25% to 35% by cholesterol-lowering therapy in patients with established coronary disease[12,33] is comparable to the mortality reductions in the bypass surgery trials; this suggests that the two forms of therapy might produce comparable results in patients at moderate risk.

High-Risk Patients

How do the results of PTCA and CABG compare with those of cholesterol lowering in patients with coronary disease who are at high risk for events? The patients with coronary disease who are at the highest risk for mortality are those with strongly positive exercise test results, those with left main coronary artery disease, and those with a markedly reduced ejection fraction.

High risk by exercise testing has been defined in a variety of ways, but the best scheme is probably that of Mark et al.[30] Using a score combining exercise time, symptoms, and degree of ST depression, they were able to define a high-risk group with an annual mortality rate of 5% to 10%. In patients with left main coronary artery disease who are medically treated, the mortality rate at 2 years is approximately 40%.[37] The 2-year mortality rate in patients with severely reduced ejection fractions due to ischemic heart disease is approximately 40%.

Davey Smith et al[38] demonstrated increasing mortality benefit from cholesterol lowering with increasing risk of cardiac mortality. At most, the reduction in mortality was 1.65 per 100 patient-years of treatment. This mortality reduction is unlikely to be an adequate strategy for the high-risk subsets described above.

TOTAL MORTALITY

How do the effects of PTCA and CABG on total mortality compare with those for cholesterol lowering? In discussing the possible benefits associated with any therapy to be applied to a large population, the total mortality effects of the therapy must be assessed. With respect to PTCA, the ACME Trial[21] was not designed to answer questions about the mortality effects of PTCA; no other studies comparing PTCA and medical therapy are available, to my knowledge. Total mortality was used as an end point in the large-scale studies of CABG compared with medical therapy, with benefit for CABG being shown in some subgroups, as discussed above.

The trials of cholesterol lowering do not provide similar answers about the effects of treatment on total mortality. Meta-analyses of these trials[12,33,39-41] have alerted us to the possibility that some or all of the available cholesterol-lowering therapies might increase noncoronary mortality. In some populations in which a decrease in coronary mortality with cholesterol lowering is small, the benefit could be offset by an increase in noncoronary mortality, producing no net benefit on total mortality.[38] Any strategy with cholesterol lowering as an alternative to revascularization must be held to a standard of decreasing total mortality.

COST COMPARISON

How do the costs associated with PTCA and CABG compare with those for cholesterol lowering? Until fairly recently, new treatments have entered clinical practice when there has been reasonable evidence that the morbidity and mortality benefits of the treatment are greater than the risk of adverse outcome attributable to the treatment. As total national expenditures on health care increase, however, standards for the acceptance of treatments are changing. It is no longer enough to consider the magnitude of morbidity and mortality reductions attributable to a treatment; the marginal cost of those reductions must also be weighed. As outlined by Eisenberg,[42] such an analysis ideally weighs both the cost and the value of the achieved outcome. Costs include direct costs, both medical and nonmedical, and indirect costs, attributable to both morbidity and premature mortality. Data comparing CABG and PTCA are available.

Reeder et al[43] studied hospital charges over 1 year, and found them to be 15% lower for PTCA when compared with CABG in patients with single-vessel disease at a single center. The authors state that a major component of the expense in the angioplasty group was the treatment of restenosis. Jang et al[44] used charge data from 11 centers, and estimated a savings of nearly 50% with PTCA. Their study, however, investigated charges only during the initial hospitalization, and estimated subsequent charges from estimates of restenosis rates. Cohen et al[45] used slightly better methodology, in that costs rather than hospital charges were used. They found mean costs of $20 937 for CABG and of $5396 for PTCA. This analysis did not take long-term costs associated with restenosis into account. No study that I know of to date has estimated nonmedical costs.

A study by Mark et al[46] provides some information about indirect costs. They observed 1252 patients after catheterization had demonstrated significant coronary artery disease. Although the patients who had had PTCA returned to work sooner, by 1 year the return-to-work rates adjusted for baseline differences in severity of disease were the same for medical therapy, PTCA, and CABG. These data, when combined with the data from the studies cited above, support but do not prove the contention that PTCA is more cost-effective than CABG if nonmedical costs and indirect costs are factored in. The data also raise the question as to whether medical therapy is more cost-effective than PTCA. Many other indirect costs beyond return-to-work rates are associated with treatment for coronary artery disease, but it is not possible to reject the notion that cost-benefit analysis might render cholesterol lowering combined with medical therapy equal or superior to revascularization. It is equally possible that a lifetime of drugs and associated office visits and laboratory tests might render cholesterol lowering a more expensive proposition.

CONCLUSIONS

The available data are not sufficient to justify changing clinical strategies to allow for using cholesterol-lowering therapy *in place of* coronary revascularization. Cholesterol lowering should continue to be used *after* revascularization when appropriate.

The available data *are* sufficient for reasonably advancing several null hypotheses that should be tested in clinical trials:

1. In patients with stable angina refractory to medication, adequate cholesterol lowering (ie, to levels similar to those in the quantitative angiographic studies demonstrating stabilization or regression) will result in symptom control at 1 year equal to that of CABG or PTCA.
2. In patients with asymptomatic ischemia after MI, adequate cholesterol lowering will result in cardiovascular morbidity and mortality at 2 years equal to that of CABG or PTCA.
3. In patients with coronary artery disease at intermediate risk of adverse cardiac events as judged by clinical or exercise test variables, adequate cholesterol lowering will result in total mortality at 2 years equal to that of CABG or PTCA.
4. In patients in the above three categories, adequate cholesterol lowering will result in total direct and indirect health care costs equal to those of PTCA or CABG.

Although large-scale randomized trials are necessary for adequate testing of these hypotheses, they would be expensive and difficult to carry out because they would require small sample sizes. Smaller-scale studies may provide evidence to support these hypotheses, and may make the undertaking of large studies more justifiable. Examples of such small-scale studies are (1) intracoronary ultrasound studies to examine changes in lesion structure over time, (2) serial coronary blood flow measurements to examine the effects of small changes in lesion dimension and shape on coronary flow, and (3) studies to examine the effects of antihyperlipidemic medi-

cation on angina in patients who are receiving medical therapy. While cholesterol-lowering therapy may herald a new era in the treatment of coronary disease, the promise of that era has not yet been fully realized.

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